Lecture Title:
ANTIBIOTICS

(Foundation Block, Microbiology)

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Lecture Objectives..

- **By the end of this lecture the student should be able to:**
- Define antibiotic ,chemotherapy and selective toxicity
- Describe the difference between bactericidal and bacteriostatic antibiotics
- Recognize the narrow and broad spectrum antibiotics
- Define the therapeutic index

Lecture Objectives..

- Know the mechanism of action of antimicrobial agents.
- Recognize the various classes of antimicrobial agents(action, spectrum and side effects)
- Explain the criteria for an ideal antimicrobial

ANTIMICROBIAL AGENTS

ANTIBIOTICS:

- Natural compounds produced by microorganism which inhibit the growth of other microorganism .

CHEMOTHERAPY:

- Synthetic compounds .

- Antimicrobial agents.

SELECTIVE TOXICITY:

- The ability to kill or inhibit the growth of a microorganism without harming the host cells.

Activity

BACTERICIDAL : kills bacteria

BACTERIOSTATIC : prevents multiplication.

Spectrum of activity

- Broad spectrum : Gram positive & Gram negative bacteria
- Narrow spectrum : selected organism.

THERAPEUTIC INDEX:

- The **RATIO** of the dose toxic to the host to the effective therapeutic dose.

- ***Examples:***

  Penicillin: High

  Aminoglycosides : low

  Polymyxin B : the lowest

MECHANISMS OF ACTION OF ANTIMICROBIALS

1) Inhibition of cell wall synthesis.

2) alteration of cell membrane

3) Inhibition of protein synthesis

4) Inhibition of nucleic acid synthesis

5) Anti-metabolite OR competitive antagonism.

ANTIMICROBIALS THAT INHIBIT CELL WALL SYNTHESIS

- 1- Beta –Lactam antimicrobial agents
- Penicillins
- Cephalosporins
- Cephamycin
- Carbapenems (imipenem & meropenem)
- Monobactam (aztreonam)
- Beta-lactamase inhibitors

2- **Vancomycin** (Teicoplanin)

β ~ LACTAM ANTIBIOTICS:

- Contain : Beta~ Lactam ring & organic acid.
- Natural & Semi~synthetic
- Bactericidal
- Bind to *PBP*, interfere with trans~peptidation reaction

Toxicity: mainly;

- hypersensitivity
- Anaphylaxis ,
- Diarrhea, ..etc

Penicillins:

Benzyl penicillin –

~ Penicillin V

- Procaine penicillin
- Benzathine penicillin

Isoxazolyl penicillins : cloxacillin – *Staph.*

Amino-penicillins ~ampicillin –*Enterobacteria.*

Acylaminopenicillins: piperacillin,mezlocillin~ *Psudomonas.*

CEPHALOSPORINS:

First Generation:

Cephradine

Ceohalexine

Second generation:

Cefuroxime

Cephamycin (Cefoxitin)

Third generation:

expanded spectrum

- eg. Ceftriaxone
- Ceftazidime

Fourth generation:

- Cefepim

- ***Fourth generation:***
- Ceftobiprole

β-Lactamase inhibitors

- β-Lactams with no antibacterial activity
- Irreversibly bind to β-lactamase enzyme
- Clavulanic acid, Sulbactam, Tazobactam
- Effective on staph. Penicillinases and broad spectrum β-lactamases.
- eg. amoxicillin/clavulanic acid, ticarcillin /clavulanic acid and piperacillin /tazobactam.

VANCOMYCIN

- Glycopeptides
- Bactericidal .Acts on Gram positive bacteria only.
- Inhibit cell wall synthesis
- Given by injection only.
- Used for *MRSA* ,*S.epidermidis*, pseudomembranous colitis.
- Red man syndrome ,phlebitis, nephrotoxic & ototoxic.

ANTIBIOTICS THAT ALTER CELL MEMBRANES

- Polymyxin B and Colistin

- Polymyxin B :a Peptide active against Gram negative bacteria only.
- Bactericidal.
- Only used *LOCALLY* due to serious nephrotoxicity
- Colistin used for the treatment of multi-resistant organisms (MRO) such as :*Pseudomonas* and *Acinetobacter* infections.

ANTIBIOTICS THAT INHIBIT PROTIEN SYNTHESIS

- AMINOGLYCOSIDES S30S ribosomal subunit
- TETRACYCLINE S30S ribosomal subunit
- CHLORAMPHENICOL 50 Sub Unit of 23 r RNA
- MACROLIDES 50 Sub Unit of 23 r RNA

AMINOGLYCOSIDES:

- Bactericidal
- Acts only on Gram negative bacteria
- Streptococci & anaerobes are naturally resistant
- Examples: Gentamicin ,Amikacin , Neomycin ,
- Given by injection .
- Nephrotoxic & Ototoxic ~ dose related.

TETRACYCLINES

- Broad spectrum , bacteriostatic
- Oral absorption
- Intracellular organisms eg. *Mycoplasma, Chlamydia ,Brucella* also for *V. cholera & Nocardia*

Classes:

- Short acting: Tetracycline
- Long acting: Minocycline , *Doxycycline* (CSF penetration).
- New tetracycline : ***Tigycycline*** *(MRSA,MSSA, some Gram negative bacteria and anaerobes.*
- **Side effects :**
- Teeth discoloration , GIT disturbance

CHLORAMPHENICOL

- Broad spectrum ,bactericidal
- Affects bone marrow cells and cause a plastic anemia

- Used for severe infections not responding to treatment , also for Rickettsial diseases.

MACROLIDES:

- Erythromycin & Clindamycin
- Bacteriostatic
- Legionella, Camylobacter, Gram negative and positive infections for patients allergic to Penicillins and Cephalosporins.
- Clindamycin acts on anaerobes as well
- Cause GIT disturbance, Pseudomembraneous colitis.
- New Macrolides :
- Azithromycin & Clarithromycin .

ANTIMICROBIALS THAT ACT ON NUCLEIC ACID

- Rifampicin
- Quinolones
- Metronidazole

RIFAMPICIN:

- Semi-synthetic, bactericidal , acts on Gram positive bacteria and selected Gram negative bacteria.
- Reserved for Tuberculosis
- Resistance develops quickly
- Used in combination
- Causes discoloration of body fluids & hepatotoxicity

QUINOLONES:

- Synthetic, bactericidal, inhibit DNA *Gyrase* and /or topoisomerase.
- **Generations:**
- *first generation*: nalidexic acid –locally acting
- *Second generation*: fluoroquinolones eg. ciprofloxacin, norfloxacin, ofloxacin,levofloxacin
- *Third generation*: sparfloxacin, gatifloxacin
- *Fourth generation*: moxifloxacin, trovafloxacin

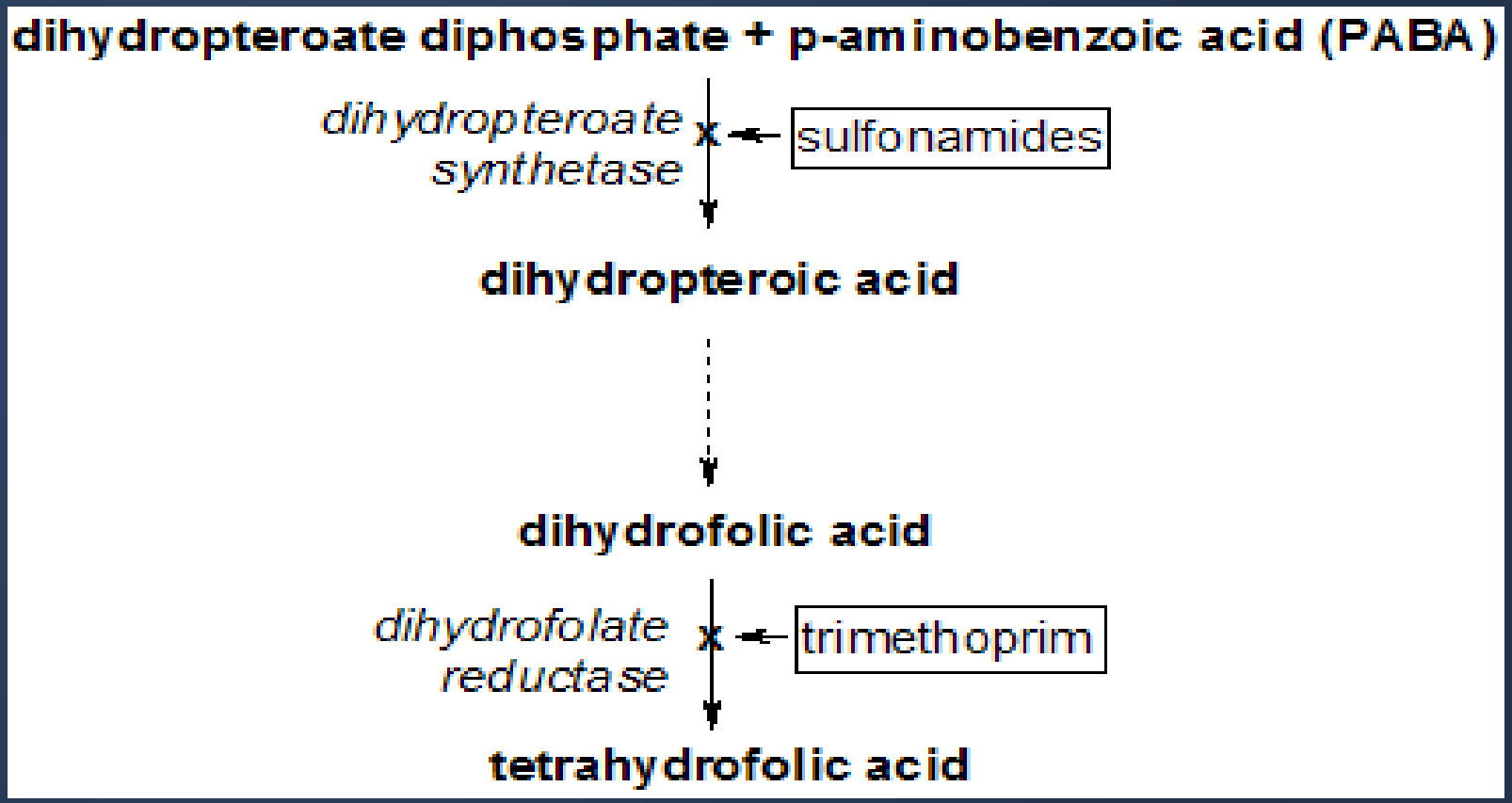
- **Side effects:** on cartilage & heart

Metronidazole

- Nitroimidazole active on anaerobic bacteria, and parasite
- Caused DNA breakage
- Used for *B.fragilis* , *Trichomonas vaginalis* , amoebiasis and giardiasis.

ANTIMETABOLITES (folate inhibitor s):

- Trimethoprim-Sulfamethoxazole (TMP-SMX)
- *Combination of TMP-SMX called* : Bactrim / Septrin
- Block sequential steps in folic acid synthesis
- *Used to treat :Nocardia, Chlamydia, Protozoa & P.cranii*
- UTI, LRTI, OM., Sinusitis, infectious diarrhea.
- Side effects: GIT, hepatitis , bone marrow depression, hypersensitivity


dihydropteroate diphosphate + p-aminobenzoic acid (PABA)
dihydropteroate synthetase
sulfonamides
dihydropteroic acid
dihydrofolic acid
dihydrofolate reductase
trimethoprim
tetrahydrofolic acid

ANTITUBERCULOUS AGENTS

First line:

- INH
- RIFAMPICIN
- ETHAMBUTOL
- PYRAZINAMIDE

Second line:

- STREPTOMYCIN
- PASA
- CYCLOSERINE,
- CAPREOMYCIN

ISONIAZIDE (INH)

- Bactericidal
- Affects mycobacteria at different sites of lung tissues
- Used for the treatment & prophylaxis of tuberculosis

- Cause peripheral neuritis(pyridoxine (vitamin B6)

Ethambutol

- BACTERICIDAL
- CONCENTRATED IN PHAGOLYSOSOME OF ALVEOLI
- OPTIC NEURITIS

Pyrazinamide

- ACID ENVIRONMENT OF MACROPHAGES
- HEPATITIS & ARTHRALGIA

ANTIBIOTIC RESISTANCE IN BACTERIA

- INDISCRIMINATE USE OF ANTIMICROBIALS
- SELECTIVE ADVANTAGE OF ANTIBIOTICS

TYPES OF RESISTANCE:

PRIMARY:

- Innate eg. *Streptococcus* & anaerobes are resistant to gentamicin.

ANTIBIOTIC RESISTANCE IN BACTERIA (Continue)

Acquired resistance :

- 1- **MUTATION**: MTB RESISTANT TO SRTEPTOMYCIN
- 2- **GENE TRANSFER**: plasmid mediated or through transposons

Cross resistance :

- Resistance to one group confer resistance to other drug of the same group .
- eg. Resistance to erythromycin and clindamycin

Dissociate resistance:

- resistance to gentamicin does not confer resistance to tobramicin .

MECHANISMS OR RESISTANCE

1~ Permeability changed

2~ modification of site of action, eg. **MUTATION**

3~ inactivation by enzymes . eg. Beta~ Lactamase & aminoglycoside inactivating enzymes

4~ passing blocked metabolic reaction eg. *PABA*~~~~~~ ⇨ ~~~folic acid , plasmid mediated.

PRINCIPLES OF ANTIMICROBIAL THERAPY:

- INDICATION
- CHOICE OF DRUG
- ROUTE
- DOSAGE
- DURATION
- DISTRIBUTION
- EXCRETION
- TOXICITY
- COMBINATION
- PROPHYLAXIS:

SHORT TERM:

- MENINGITIS

LONG TERM:

- TB, UTI , RHEUMATIC FEVER

CRITERIA FOR IDEAL ANTIMICROBIAL:

- SELECTIVE TOXICITY
- NO HYPERSENSITIVITY
- PENETERATE TISSUES QUICKLY
- RESISTANCE NOT DEVELOP QUICKLY
- NO EFFECT ON NORMAL FLORA
- BROAD SPECTRUM

Reference book and the relevant page numbers..

- **Sherries Medical Microbiology, an introduction to Infectious Diseases.** Latest edition, Kenneth Ryan and George Ray. Publisher: Mc Graw Hill.

Thank You ☺

(Foundation Block, Microbiology)